



05/24/04

IPV AF/1616
\$

Attorney's Docket No.9448.50

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Leonard
Serial No.: 10/041,916
Filed: January 8, 2002

Confirmation No.: 4094
Group Art Unit: 1616
Examiner: Badio, B.

For: SYNTHESIS OF A MIXTURE OF SULFATE ESTROGENS USING A
SULFURTRIOXIDE COMPLEX

Date: May 21, 2004

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**TRANSMITTAL OF APPEAL BRIEF
(PATENT APPLICATION--37 C.F.R. § 1.192)**

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF for the above-identified application, pursuant to the Notice of Appeal filed on February 24, 2004.

2. This application is filed on behalf of
☐ a small entity.

3. Pursuant to 37 C.F.R. § 1.17(c), the fee for filing the Appeal Brief is:
☐ small entity \$165.00
☒ other than small entity \$330.00

Appeal Brief fee due \$330.00.

☒ Any additional fee or refund may be charged to Deposit Account
50-0220.

Respectfully submitted,

Devin R. Jensen
Registration No. 44,805

Myers Bigel Sibley & Sajovec, P.A.
P. O. Box 37428
Raleigh, North Carolina 27627
Telephone: (919) 854-1400
Facsimile: (919) 854-1401
Customer No. 20792

CERTIFICATE OF EXPRESS MAILING

"Express Mail" mailing label number: EV381443870US Date of Deposit:
May 21, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Betty Lou Rosser



Attorney's Docket No. 9448.50

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Leonard
Serial No.: 10/041,916
Filed: January 8, 2002

Confirmation No.: 4094
Group Art Unit: 1616
Examiner: Badio, B.

For: SYNTHESIS OF A MIXTURE OF SULFATE ESTROGENS USING A
SULFURTRIOXIDE COMPLEX

Date: May 21, 2004

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

Sir:

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed on February 24, 2004 and is filed in triplicate pursuant to 37 C.F.R. § 1.192.

REAL PARTY IN INTEREST

The real party in interest is Barr Laboratories, Inc., a New Jersey corporation having a principal place of business at 400 Chestnut Ridge Road, Woodcliff Lake, NJ, the Assignee of this application. This application was recently assigned to Barr Laboratories, Inc. by the original assignee Endeavor Pharmaceuticals, Inc.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals and/or interferences that will directly or indirectly affect this Appeal or have any bearing on the Board's decision in this Appeal.

STATUS OF CLAIMS

Claims 1-19 are pending in this case and stand rejected.

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as being obvious in light of the combination of Raijmakers et al. (U.S. Pat. No. 5,998,639), Simoons (U.S. Pat. No. 4,154,820), Raveendranath et al. (U.S. Pat. No. 5,288,717), Shah et al. (U.S. Pat. No. 6,525,039), Bender et al. (U.S. Pat. No. 5,998,638), and Kong et al. (U.S. Pat. No. 6,458,778).

STATUS OF AMENDMENTS

A Final Office Action was issued by the Office on September 24, 2003. A response to the Final Office Action was filed on December 22, 2003. The response to the Final Office Action did not propose any amendments to the claims. An Advisory Action was mailed on January 13, 2004, rejecting Claims 1-19 for the reasons of record. A Notice of Appeal was filed on February 24, 2004.

SUMMARY OF THE INVENTION

The present invention relates to processes for the synthesis of mixtures of sulfated estrogens. *See, Specification* at ¶ 1. More particularly, the processes provide for the synthesis of stable compositions of complex mixtures of sulfated estrogens. *Id.* at ¶ 6.

According to some embodiments of the invention, one or more alkali metal salts of estrogens are reacted with a sulfur trioxide complex and stabilized with tris(hydroxymethyl)aminomethane (TRIS) to yield a stabilized composition of sulfated estrogens. *Id.* at ¶ 7. The process may be performed in an apolar, aprotic solvent. *Id.* The process may also be performed in a single reaction vessel. *Id.* at ¶ 15. The alkali metal salts of estrogens according to embodiments of the present invention may include alkali metal salts of the following estrogen compounds: $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17 α -estradiol, 17 β -estradiol, 17 α -dihydroequilin, 17 β -dihydroequilin, equilenin, 17 α -dihydroequilenin, 17 β -dihydroequilenin, 17 α - $\Delta^{8,9}$ -dehydroestradiol, 17 β - $\Delta^{8,9}$ -dehydroestradiol, 6-OH equilenin, 6-OH 17 α -dihydroequilenin, 6-OH 17 β -dihydroequilenin, ethinyl estradiol, and estradiol valerate. *Id.* at ¶ 10

According to other embodiments of the invention, a mixture of two or more estrogens selected from the group consisting of: $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17 α -estradiol,

17 β -estradiol, 17 α -dihydroequilin, 17 β -dihydroequilin, equilenin, 17 α -dihydroequilenin, 17 β -dihydroequilenin, 17 α - $\Delta^{8,9}$ -dehydroestradiol, 17 β - $\Delta^{8,9}$ -dehydroestradiol, 6-OH equilenin, 6-OH 17 α -dihydroequilenin, 6-OH 17 β -dihydroequilenin, ethinyl estradiol, and estradiol valerate is reacted with an alkali metal hydride to form a mixture of alkali metal salts of estrogens. *Id.* at ¶ 7. The mixture of alkali metal salts of estrogens is then reacted with a sulfur trioxide complex and stabilized with TRIS to form a stable composition of sulfated estrogens. *Id.*

The processes according to embodiments of the invention can be used to produce mixtures of sulfated estrogens in specific ratios. *Id.* at ¶ 9. In addition, the processes according to embodiments of the invention can be performed in a single reaction vessel. *Id.* at ¶ 8.

ISSUES

1. Whether Claims 1-19 are obvious under 35 U.S.C. § 103(a) in light of the combination of Raijmakers et al. (U.S. Pat. No. 5,998,639), Simoons (U.S. Pat. No. 4,154,820), Raveendranath et al. (U.S. Pat. No. 5,288,717), Shah et al. (U.S. Pat. No. 6,525,039), Bender et al. (U.S. Pat. No. 5,998,638), and Kong et al. (U.S. Pat. No. 6,458,778).

GROUPING OF CLAIMS

The appealed claims are Claims 1-19. The following is the grouping of the claims for this Appeal:

- (a) Claims 1-8 stand and fall together;
- (b) Claims 9-14 stand and fall together; and
- (c) Claims 15-19 stand and fall together.

ARGUMENT

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as being obvious in light of a combination of six references. In particular, the processes recited in Claims 1-19 of the present application are rejected as obvious because a composition resulting from the recited

processes may be the same as a composition of a first reference (Simoons et al.), which could allegedly be made by reversing the steps proposed by a second reference (Raijmakers et al.) and using processes taught by a third (Shah) and fourth (Raveendranath) reference along with reactants taught by a fifth (Kong et al.) and a sixth reference (Bender et al.). However, the combination of references fails to support a *prima facie* obviousness rejection because none of the references, alone or in combination, teach or suggest all of the recitations of the claims or provide any motivation for the tenuous combination. For at least these reasons, Claims 1-19 are allowable over the 35 U.S.C. § 103(a) rejections.

1. The Combination of References

Each of the steps recited in the processes of the claims is allegedly known in the prior art. The Final Action alleges that the steps recited in Claims 1-19 of the present application are made obvious by a combination of six references: Simoons (U.S. Pat. No. 4,154,820), Raijmakers et al. (U.S. Pat. No. 5,998,639), Shah et al. (U.S. Pat. No. 6,525,039), Raveendranath et al. (U.S. Pat. No. 5,288,717), Bender et al. (U.S. Pat. No. 5,998,638), and Kong et al. (U.S. Pat. No. 6,458,778).

Simoons et al. proposes a “stable synthesized conjugated estrogen composition comprising one or more selected alkali metal synthetic conjugated estrogen sulfate salts” and “one or more suitable antioxidants.” *See, Simoons et al.* Abstract. Processes for forming the selected alkali metal synthetic conjugated estrogen sulfate salts used in the compositions of Simoons et al. are not taught by the reference. Instead, the compositions of Simoons et al. are formed by blending pre-made synthetically prepared estrogen conjugates. *See, Simoons et al.* at col. 7, lines 34-40. Thus, Simoons et al. does not teach or suggest processes that may be used for the production of alkali metal synthetic conjugated estrogen sulfate salts.

Raijmakers et al. proposes methods for producing “sulfated steroid mixtures containing delta(8,9)DHE through sulfatation of an estrogen mixture containing delta(8,9)DHE or derivatives thereof which can be obtained by isomerization of equilin or a derivative thereof.” *See, Raijmakers et al.* at col. 2, lines 14-19. The processes disclosed by Raijmakers et al. involve the isomerization of equilin to form relatively pure delta(8,9)DHE,

which may be converted into a sodium sulfate. *See, Id.* at col. 3, lines 46-51. The process of converting an estrogen into its sodium sulfate according to Raijmakers et al. involves the direct sulfation of the estrogen followed by the incorporation of an alkali metal. *See, Examples 12-14.* Although the sulfation reactions of Raijmakers et al. may be used to form a mixture of sulfated estrogens, Raijmakers et al. does not propose a process wherein the formation of an alkali metal salt of an estrogen occurs prior to sulfation. Nor does Raijmakers et al. suggest that the sulfation reactions could be performed in the same manner on alkali metal salts of estrogens. Thus, Raijmakers et al. proposes the formation of sodium sulfated estrogens, and especially delta(8,9)DHE, by the direct sulfation of the estrogen and not the sulfation of an alkali metal salt of the estrogen.

Kong et al. proposes compounds of estrogen ester sulfates and their uses as treatment agents. In addition, Kong et al. proposes compounds of alkali metal salts of the estrogen ester sulfates. The processes proposed by Kong et al. to form such alkali metal salts of the estrogen ester sulfates involve the sulfation of an estrogen alcohol dissolved in tetrahydrofuran (THF) through the treatment with triethylamine-sulfur trioxide complex followed by the treatment of the sulfated estrogen with sodium hydroxide. *See, Kong et al.* at col. 13, lines 35-43. This process is similar to that disclosed by Raijmakers et al. Kong et al. does not propose processes for reacting sulfur trioxide complexes with an alkali metal salt of an estrogen.

Bender et al. proposes compounds of a single estrogen sulfate ester or a salt thereof and methods for treating ailments using such compounds. The sulfate esters of Bender et al. are also formed by the sulfation of an estrogen. In those instances where Bender et al. proposes an alkali metal salt of an estrogen sulfate ester, the estrogen sulfate ester is reacted with sodium hydroxide to form the alkali metal salt. Bender et al. does not propose the sulfation of an alkali metal salt of estrogen.

Shah proposes the formation of various compounds of pharmaceutically acceptable salts of single estrogen sulfate esters or alkali metal salts of a single estrogen sulfate ester, including compounds "consisting essentially of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt." *See, Shah* at col. 1, lines 65-66. The formation of the sulfated estrogen

ester sodium salt proposed by Shah involves the simultaneous reaction of an estrogen with sodium hydride, a triethylamine-sulfurtrioxide complex, and a sodium hydroxide solution to produce 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt, a particular alkali metal salt of an estrogen sulfate ester. *See, Shah* at Scheme 1 and Example 1. Shah does not propose the reaction of a mixture of alkali metal salts of estrogens with a sulfur trioxide complex.

Raveendranath proposes “a process for the production of the alkali metal 8,9-dehydroestone sulfate esters and their stabilized compositions.” *See, Raveendranath* at col. 1, lines 43-46. The proposed process involves the “production of an alkali metal salt of 8,9-dehydroestrone followed by sulfation with trimethylaminesulfurtrioxide under mild conditions in a polar, aprotic solvent such as tetra-hydrofuran with simultaneous or subsequent addition of tris(hydroxymethyl)aminomethane as a stabilizer.” *See, Id.* at col. 1, lines 53-59. The sulfation of other alkali metal salts of estrogens is not proposed and Raveendranath indicates that the compounds formed from the process of Raveendranath are “free from other conjugated esters present in material found in natural sources of mixed esters.” *See, Id.* at col. 1, lines 38-40.

2. 35 U.S.C. § 103(a) Rejection based on the Combination of References

A *prima facie* obviousness rejection of a claim is only supported if certain criteria are met; in particular:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, **there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.** Second, there must be a reasonable expectation of success. Finally, **the prior art reference (or references when combined) must teach or suggest all the claim limitations.** The teaching or suggestion to make the claimed combination and the reasonable expectation of success **must both be found in the prior art**, and not based on applicant’s disclosure.

See, M.P.E.P. §2142, citing In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)(emphasis added). A *prima facie* obviousness rejection of Claims 1-19 is not supported by the combination of references because the references fail to teach or suggest all of the

recitations of Claims 1-19 and the references fail to motivate a combination that teaches all or suggest all of the recitations.

(a) Claims 1-8

Claims 1-8 stand and fall together. In particular, Claims 2-8 stand and fall with Claim 1, which recites, in part:

1. A process for the production of a stable composition comprising a mixture of sulfated estrogens, the process comprising the steps of: (a) reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens...(emphasis added).

Claim 1 is not obvious because the combination of references fails to teach or suggest a process as recited in Claim 1. None of the references teach or suggest a process for producing a mixture of sulfated estrogens wherein the process involves reacting a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens as recited in Claim 1.

The Final Action alleges that Claim 1 is obvious in light of the combination of references because Simoons et al., Rajmakers et al., Kong et al., and Bender et al. teach a method for the preparation of a mixture of alkali metal salts of estrogen sulfates. In addition, the Claims are rejected as being obvious because Shah and Raveendranath allegedly teach the production of alkali metal salts of estrogen sulfates.

Simoons et al. fails to teach or suggest the recitations of Claim 1. Simoons et al. proposes a composition having at least one alkali metal sulfate salt but it does not propose a process for forming such a composition. Claim 1 recites a process. The composition of Simoons et al. does not make obvious a process.

The Final Action admits that three of the references fail to teach or suggest a process as recited in Claim 1. The Final Action states that “unlike, Rajmakers et al., Kong and Bender, the claimed process recites sulfatation of the alkali metal salts of estrogens or production of the alkali metal salts of estrogens followed by sulfatation.” *See, Final Action* at p. 3. Claim 1 includes recitations that are not taught or suggested by those three references

and is not made obvious by the combination of those references. A combination of Simoons et al. with Raijmakers et al., Kong et al., and Bender et al. fails to teach or suggest all of the recitations of Claim 1, thereby failing to provide support for a *prima facie* obviousness rejection. *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Furthermore, Claim 1 recites a process for forming a mixture of sulfated estrogens. Kong et al. and Bender et al. do not teach or suggest the formation of a mixture of sulfated estrogens. Instead, Kong et al. and Bender et al. propose the formation of a single sulfated estrogen or an alkali metal salt thereof and its use in the treatment of estrogen deficiencies. The Final Action recognizes this fact. *See, Final Action* at p. 3. According to the references, the formation and use of a single sulfated estrogen is preferred to the use of a mixture such as Premarin®. The proposed formation of a single sulfated estrogen or alkali metal salt thereof does not make obvious the formation of a mixture of sulfated estrogens.

The Final Action also alleges that Claim 1 is obvious because “utilizing the process taught by Shah and Raveendranath would be *prima facie* obvious” in light of the composition of Simoons et al. and the reverse steps taught by Raijmakers et al. *See, Final Action* at p. 3. However, neither Shah nor Raveendranath propose a process for forming mixtures of sulfated estrogens as recited in Claim 1.

Shah proposes pharmaceutically acceptable salts of 3 β -hydroxy-5,7,9-estratriene-17-one 3- sulfate ester, alkali metal salts of the same, and processes for forming such salts. Shah does not propose processes for producing mixtures of estrogen sulfate esters or their alkali metal salts. The failure of Shah to propose a process for forming mixtures of sulfated estrogens as recited in Claim 1 precludes a *prima facie* obviousness rejection. *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The processes of Shah are illustrated by Scheme 1. In one process, the compounds of Shah are produced by methods similar to those proposed by Raijmakers et al., Kong et al., and Bender et al., wherein the estrogen is first sulfated and then reacted with sodium hydroxide to form an alkali metal salt of the sulfated estrogen ester. This process does not make obvious the recitations of Claim 1 for the same reasons that the Raijmakers et al., Kong et al., and Bender et al. fail to make obvious Claim 1. In a second process, a simultaneous

reaction of an estrogen with sodium hydride, a triethylamine-sulfur trioxide complex, and a sodium hydroxide solution produces an alkali metal salt of the sulfated estrogen ester. Shah does not propose the reaction of a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens as recited in Claim 1. Thus, Shah fails to make obvious the recitations of Claim 1.

Raveendranath does not propose processes for forming mixtures of sulfated estrogens as recited in Claim 1. Raveendranath explicitly proposes that the compounds formed from the process of Raveendranath are “free from other conjugated esters present in material found in natural sources of mixed esters.” *See, Id.* at col. 1, lines 38-40. Because Raveendranath does not teach or suggest the formation of mixtures of sulfated estrogens by the process recited in Claim 1, Raveendranath does not support a *prima facie* obviousness rejection of Claim 1.

None of the references cited in the Final Action support a *prima facie* obviousness rejection of Claim 1 because none of the references, alone or in combination, teach or suggest all of the recitations of Claim 1. Simoons et al. discloses compositions but no processes. Rajmakers et al., Kong et al., and Bender et al. fail to teach or suggest the process recited in Claim 1, instead proposing the reaction of a sulfated estrogen with an alkali to form an alkali metal salt of the sulfated estrogen. Shah proposes a process similar to Rajmakers et al. and a process wherein an estrogen is reacted with a sulfur trioxide complex and an alkali simultaneously. Finally, Raveendranath fails to propose a process for forming mixtures of sulfated estrogens. The failure of the references to teach or suggest “reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens,” as recited in Claim 1 precludes a *prima facie* obviousness rejection because the third requirement for a *prima facie* rejection is not satisfied. *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The *prima facie* obviousness rejection of Claim 1 also fails because there is no motivation in the references, or in the art, to combine and alter the references to make obvious the recitations of Claim 1. The lack of motivation precludes a *prima facie* obviousness rejection of the claims.

The Final Action indicates that the processes of Shah and Raveendranath, when combined with the teachings of the other references, provide sufficient support for a *prima facie* obviousness rejection of Claim 1. In particular, Simoons et al. and Raijmakers et al. are relied upon to provide the motivation to form a mixture of sulfated estrogens using the processes of Shah and Raveendranath. However, the processes of Shah are similar to those of Raijmakers et al., which the Final Action admits are “unlike...the claimed process.” Thus, even if Simoons et al. and Raijmakers et al. motivate the formation of a mixture of sulfated estrogens using the processes proposed by Shah, which they do not, the combination does not teach or suggest the reaction of “a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens” as recited in Claim 1.

Simoons et al. and Raijmakers et al. do not motivate the formation of a mixture of sulfated estrogens as recited in Claim 1 if combined with Raveendranath. The composition formed by the process of Raveendranath is an alkali metal salt of 8,9-dehydroestrone sulfate ester. The composition mixtures of Simoons et al. do not include alkali metal salts of 8,9-dehydroestrone sulfate esters. Therefore, a person of skill in the art would not combine the product of Raveendranath in a composition mixture of Simoons et al. because Simoons et al. does not propose that 8,9-dehydroestrone sulfate esters are desired in such a mixture. In addition, the processes for forming 8,9-dehydroestrone according to Raveendranath “differs from methods generally involved in the sulfation of steroids” because the “reported methods for sulfation of steroids proved ineffective in the sulfation of 8,9-dehydroestrone.” *See, Raveendranath* at col. 1, lines 46-53. The difference in sulfation methods taught by Raveendranath and the exclusion of 8,9-dehydroestrone from the Simoons et al. composition tends to motivate a mutual exclusion between Raveendranath and Simoons et al. rather than a combination of the two references. The lack of motivation to combine the references precludes a *prima facie* obviousness rejection.

A lack of motivation to combine Raveendranath with Raijmakers et al. also exists. Raveendranath proposes that its compositions are formed “free from other conjugated esters,” which teaching conflicts with Raijmakers et al. proposal of mixtures containing

delta(8,9)DHE. Raveendranath also indicates that its process is different than those processes wherein the sulfation is “carried out by treatment of the steroid with amine-sulfur trioxide complexes followed by treatment with a cation exchange resin mediated by strong alkaline bases, preferably in hydroxylic solvents.” *See, Raveendranath* at col. 1, lines 46-51. This distinguishes Raveendranath from Raijmakers et al. because the process of Raijmakers et al. is “ineffective in the sulfation of 8,9-dehydrostrone.” *See, Id.* at col. 1, lines 52-53. The processes of Raveendranath and Raijmakers et al. are not compatible. No motivation exists to combine Raveendranath and Raijmakers et al. to support a *prima facie* obviousness rejection of Claim 1.

The lack of motivation to combine the references to arrive at a process that includes “reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens” as recited in Claim 1 precludes a *prima facie* obviousness rejection of that Claim. *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). In addition, the failure of the references, alone or in combination, to teach or suggest processes for producing mixtures of sulfated estrogens in the manner recited by Claim 1 precludes a *prima facie* obviousness rejection of Claim 1. *See, Id.* Claim 1 is allowable over the rejections of record.

Claims 2-8 stand and fall with Claim 1. Claims 2-8 depend from Claim 1. As dependent claims of a nonobvious independent claim, Claims 2-8 are also nonobvious. *See, In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)(stating that if an independent claim is nonobvious under 35 U.S.C. § 103 then any claim depending therefrom is nonobvious); *see also*, M.P.E.P. § 2143.03.

(b) Claims 9-14

Claim 9 depends from Claim 1 but stands and falls apart from Claim 1. Claims 9-15 stand and fall together. More particularly, Claims 10-14 stand and fall with Claim 9, which recites, in part, the step of “obtaining the mixture of alkali metal salts of estrogens by reacting a mixture of estrogens with an alkali metal hydride in an apolar, aprotic solvent.” The combination of references fails to teach or suggest the formation of a mixture of alkali metal

salts of estrogens in such a manner, thereby precluding a *prima facie* obviousness rejection of Claims 9-12 and 14.

Raveendranath proposes a process that includes “the initial production of an alkali metal salt of 8,9-dehydroestrone followed by sulfation with trimethylaminesulfurtrioxide under mild conditions in a polar, aprotic solvent.” *See, Raveendranath* at col. 1, lines 53-59. However, Raveendranath does not propose a process for obtaining a mixture of alkali metal salts by reacting a mixture of estrogens with an alkali metal hydride in an apolar, aprotic solvent as recited by Claim 9. The lack of such teaching precludes a *prima facie* obviousness rejection because Raveendranath fails to teach or suggest all of the recitations of Claim 9. *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The combination of references cited by the Final Action also fails to teach or suggest all of the recitations of Claim 9 because none of the other references teach a process similar to that recited in the claim.

Furthermore, there is no motivation to alter Raveendranath or combine Raveendranath with the other references to make obvious Claim 9. Raveendranath teaches away from a combination with Simoons et al. and Raijmakers et al. for the same reasons as previously stated. In addition, Raveendranath teaches away from the formation of a mixture of alkali metal salts of estrogens, instead teaching that its process be used to create a product “free from other conjugated esters.” *See, Raveendranath* at col. 1, lines 38-40. The lack of motivation to combine references with the process of Raveendranath and its teachings away from such a combination precludes a *prima facie* obviousness rejection of Claim 9. *See, In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Claims 10-14 stand and fall with Claim 9. Claims 10-14 depend from Claim 9. As dependent claims of a nonobvious independent claim, Claims 10-14 are also nonobvious. *See, In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)(stating that if an independent claim is nonobvious under 35 U.S.C. § 103 then any claim depending therefrom is nonobvious); *see also*, M.P.E.P. § 2143.03.

(c) Claims 15-19

Claims 15-19 stand and fall together, and in particular, dependent Claims 16-19 stand and fall with independent Claim 15. Claim 15 recites, in part:

15. A process for the production of a stable composition comprising a mixture of sulfated estrogens, the process comprising the steps of: (a) reacting a mixture of at least two estrogens with sodium hydride in an apolar, aprotic solvent to provide a mixture of alkali metal salts of the estrogens; b) reacting sulfur trioxide-trimethylamine with the mixture of alkali metal salts of estrogens in an apolar, aprotic solvent to provide a mixture of sulfated alkali metal salts of estrogens...(emphasis added).

The combination of references fails to teach or suggest all of the recitations of Claim 15, thereby failing to support a *prima facie* obviousness rejection.

Claim 15 includes the recitations of “reacting a mixture of at least two estrogens with sodium hydride in an apolar, aprotic solvent” which is not taught or suggested by the cited references. Raveendranath proposes a method whereby a single estrogen, 8,9-dehydroestrone, is reacted to form an alkali metal salt of dehydroestrone but it does not propose the reaction of a mixture of at least two estrogens. In fact, Raveendranath teaches away from a reaction of more than one estrogen because its products are to be “free from other conjugated esters.” *See, Raveendranath* at col. 1, lines 38-40. The lack of teaching or suggestion to include the steps of reacting a mixture of at least two estrogens with sodium hydride as recited in Claim 15 precludes a *prima facie* obviousness rejection of Claim 15. *See, In re Vaack*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Additionally, there is no motivation to combine the references to make obvious the recitations of Claim 15. Raveendranath teaches away from the formation of mixtures of alkali metal salts of estrogens and away from the processes proposed by the other references. The lack of motivation to combine the references precludes a *prima facie* obviousness rejection. Claim 15 is allowable.

Claim 16-19 depend from independent Claim 15. As dependent claims of a non-obvious independent claim, Claims 16-19 are also nonobvious. *See, In re Fine*, 837 F.2d

In Re: Leonard
Serial No. 10/041,916
Filed: January 8, 2004
Page 14 of 18

1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)(stating that if an independent claim is nonobvious under 35 U.S.C. § 103 then any claim depending therefrom is nonobvious); *see also*, M.P.E.P. § 2143.03.

In Re: Leonard
Serial No. 10/041,916
Filed: January 8, 2004
Page 15 of 19

CONCLUSION

On the entire record and in view of all the cited references, Appellants submit that Claims 1-19 are nonobvious. Accordingly, it is respectfully requested that the Examiner's conclusions be reversed, and that this case be passed to issuance.

Respectfully submitted,



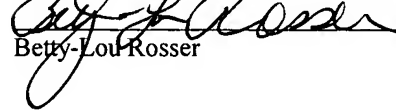
Devin R. Jensen
Registration Number 44,805

Customer No. 20792
Myers Bigel Sibley & Sajovec, P.A.
P. O. Box 37428
Raleigh, North Carolina 27627
Telephone: (919) 854-1400
Facsimile: (919) 854-1401

CERTIFICATE OF EXPRESS MAILING

"Express Mail" mailing label number: EV381443870US Date of Deposit: May 21, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.


Betty-Lou Rosser

CLAIMS APPENDIX

1. (Previously Presented) A process for the production of a stable composition comprising a mixture of sulfated estrogens, the process comprising the steps of:
 - a) reacting a sulfur trioxide complex with a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens, wherein the estrogens are selected from the group consisting of $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17α -estradiol, 17β -estradiol, 17α -dihydroequilin, 17β -dihydroequilin, equilenin, 17α -dihydroequilenin, 17β -dihydroequilenin, 17α - $\Delta^{8,9}$ -dehydroestradiol, 17β - $\Delta^{8,9}$ -dehydroestradiol, 6-OH equilenin, 6-OH 17α -dihydroequilenin, 6-OH 17β -dihydroequilenin, ethinyl estradiol, and estradiol valerate;
 - b) adding a stabilizing amount of tris(hydroxymethyl)aminomethane; and
 - c) recovering the stable composition comprising the mixture of sulfated estrogens and tris(hydroxymethyl)aminomethane.
2. (Previously Presented) The process according to claim 1 wherein the estrogens comprise at least two of $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17α -estradiol, 17β -estradiol, 17α -dihydroequilin, and 17β -dihydroequilin.
3. (Original) The process according to claim 1 wherein the sulfur trioxide complex is selected from the group consisting of sulfur trioxide-pyridine and sulfur trioxide-trimethylamine.
4. (Original) The process according to claim 1 wherein the alkali metal salt is selected from the group consisting of lithium, sodium, and potassium.
5. (Original) The process according to claim 1 wherein steps a) and b) are performed in an apolar, aprotic solvent.
6. (Original) The process of claim 5 wherein the solvent is tetrahydrofuran.

7. (Original) The process according to claim 1 wherein all steps are performed in a single reaction vessel.

8. (Previously Presented) The process according to claim 1 wherein the mixture of sulfated estrogens are produced in a specific ratio by starting with a specific ratio of at least two estrogenic compounds selected from the group consisting of $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17 α -estradiol, 17 β -estradiol, 17 α -dihydroequilin, and 17 β -dihydroequilin.

9. (Original) The process according to claim 1 further comprising the step of obtaining the mixture of alkali metal salts of estrogens by reacting a mixture of estrogens with an alkali metal hydride in an apolar, aprotic solvent.

10. (Original) The process according to claim 9 wherein the sulfur trioxide complex is selected from the group consisting of sulfur trioxide-pyridine and sulfur trioxide-trimethylamine.

11. (Original) The process according to claim 9 wherein the alkali metal salt is selected from the group consisting of lithium, sodium, and potassium.

12. (Original) The process according to claim 9 wherein the apolar, aprotic solvent is tetrahydrofuran.

13. (Original) The process according to claim 9 wherein all steps are performed in a single reaction vessel.

14. (Previously Presented) The process according to claim 9 wherein the sulfated estrogens are produced in a specific ratio by starting with specific ratios of estrogenic compounds selected from the group consisting of $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17 α -

estradiol, 17 β -estradiol, 17 α -dihydroequilin, and 17 β -dihydroequilin.

15. (Previously Presented) A process for the production of a stable composition comprising a mixture of sulfated estrogens, the process comprising the steps of:

- a) reacting a mixture of at least two estrogens with sodium hydride in an apolar, aprotic solvent to provide a mixture of alkali metal salts of the estrogens;
- b) reacting sulfur trioxide-trimethylamine with the mixture of alkali metal salts of estrogens in an apolar, aprotic solvent to provide a mixture of sulfated alkali metal salts of estrogens;
- c) adding a stabilizing amount of tris(hydroxymethyl)aminomethane; and
- d) recovering the stable composition comprising the mixture of sulfated estrogens and tris(hydroxymethyl)aminomethane.

16. (Previously Presented) The process according to claim 15 wherein the mixture of estrogens comprises at least two estrogenic compounds selected from the group consisting of $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17 α -estradiol, 17 β -estradiol, 17 α -dihydroequilin, and 17 β -dihydroequilin.

17. (Original) The process according to claim 15 wherein the apolar, aprotic solvent is tetrahydrofuran.

18. (Original) The process according to claim 15 wherein all steps are performed in a single reaction vessel.

19. (Previously Presented) The process according to claim 15 wherein the sulfated estrogens are produced in a specific ratio by starting with a specific ratio of at least two estrogenic compounds selected from the group consisting of $\Delta^{8,9}$ -dehydroestrone, estrone, equilin, 17 α -estradiol, 17 β -estradiol, 17 α -dihydroequilin, and 17 β -dihydroequilin.